Effective and Safe Combination Therapy for Severe Acne Vulgaris: A Randomized, Vehicle-Controlled, Double-blind Study of Adapalene 0.1%–Benzoyl Peroxide 2.5% Fixed-Dose Combination Gel With Doxycycline Hyclate 100 mg

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There is a paucity of treatment options for severe acne vulgaris aside from oral isotretinoin. This randomized, vehicle-controlled, multicenter, double-blind study evaluated the efficacy and safety of combination therapy using adapalene 0.1%–benzoyl peroxide 2.5% (A/BPO) fixed-dose combination gel with doxycycline hyclate 100 mg in the treatment of severe acne vulgaris. A total of 459 participants were randomized in a 1:1 ratio to receive oral doxycycline hyclate 100 mg once daily and either A/BPO or vehicle once daily for 12 weeks. Efficacy in the A/BPO with doxycycline group was demonstrated as early as week 2 compared with the vehicle arm for total, inflammatory, and noninflammatory lesions (all P*<.005). At week 12, this combination was superior to vehicle with doxycycline in reducing total, inflammatory, and noninflammatory lesion counts (an added incremental benefit of 23%, 24%, and 21%, respectively), as well as for global success and overall participant satisfaction (all* P*<.001). Digital UV fluorescence photography demonstrated a rapid reduction in* Propionibacterium acnes *in the A/BPO with doxycycline group, particularly within the first 4 weeks. These findings provide evidence on the efficacy of combining A/BPO and the oral antibiotic doxycycline in the treatment of severe acne vulgaris.*

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Dr. Eichenfield is on the advisory board for and has received grants from Galderma Laboratories, LP. Dr. Tan is an advisory board member and speaker for and has received research grants from Galderma R&D. Dr. Jorizzo is a speaker for and has received honoraria from Dermik Laboratories and Graceway Pharmaceuticals, LLC. Mr. Kerrouche and Mr. Dhuin are employees of Galderma R&D and hold a patent related to the study medication.
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Few options are available in the treatment of severe acne vulgaris aside from oral isotretinoin. It is the only medication that affects all major

acne pathogenic factors[1] and is the treatment of choice for severe forms of acne, including recalcitrant nodular acne or acne conglobata.[2] However, few other treatments are currently standardized for severe (not nodulocystic) acne, as specified by the investigator's global assessment (IGA) scale. Although definitions of acne severity vary, the IGA is a reliable and practical tool that typically is employed in clinical trials for acne drug registration.[3] According to the IGA categories in our study, severe acne can be defined as involvement of the entire face, whereby it is covered with many papules and pustules, open or closed comedones, and rare nodules.

In the treatment of all but the most severe recalcitrant acne vulgaris, the combination of a topical retinoid and benzoyl peroxide (BPO) with an oral antibiotic has been recommended as first-line therapy.[2,4] With oral antibiotics, the potential for antibiotic resistance of *Propionibacterium acnes* and other mucocutaneous bacteria is a growing clinical concern. The addition of BPO, a broad-spectrum antimicrobial agent to which *P acnes* has not developed resistance, can prevent bacterial resistance. Furthermore, the use of a topical retinoid can target the primary acne lesion, the microcomedone.[2,5]

Accordingly, therapy using the anticomedogenic, anti-inflammatory, and comedolytic properties of adapalene[6,7] synergistically combined[8] with BPO is congruent with recommended guidelines for topical acne therapy, is effective and safe,[8-11] and does not promote the incidence of antibiotic resistance.[12] Furthermore, combination of doxycycline hyclate 100 mg and adapalene gel 0.1% led to greater and faster improvement compared to the oral antibiotic alone among participants with severe acne.[13]

If inadequately treated, acne may cause serious physical and emotional scarring that can substantially impact the patient's quality of life.[2] Therefore, it is important to provide a therapy for severe acne that quickly and effectively improves the condition and is associated with few potentially serious adverse effects.

The objective of this study was to evaluate the efficacy and safety of adapalene 0.1%–BPO 2.5% (A/BPO) gel or its vehicle with doxycycline hyclate 100 mg in the treatment of severe acne vulgaris.

Methods

Study Design—The efficacy and safety of A/BPO with doxycycline were compared with vehicle with doxycycline in a randomized, vehicle-controlled, multicenter, double-blind, parallel group study conducted at 30 centers in the United States and 5 centers in Canada between August 18, 2008, and February 18, 2009. Participants were randomized in a 1:1 ratio to receive oral doxycycline hyclate 100 mg once daily in the morning and either A/BPO or vehicle once daily in the evening for 12 weeks. Additionally, daily facial moisturizer with sun protection factor 15 and gentle skin cleanser use was encouraged. Integrity of the blinding was ensured by packaging the topical medications in identical tubes and requiring a third party other than the investigator/evaluator to dispense them. Efficacy and safety evaluations were performed at baseline and at weeks 2, 4, 8, and 12. Urine pregnancy tests were mandatory for all female participants of childbearing potential at baseline and week 12, or earlier in cases of early discontinuation. Participants could withdraw from the study at any time and were to be fully evaluated when possible upon discontinuation.

This study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practices and in compliance with local regulatory requirements, and was both reviewed and approved by institutional review boards. All participants provided written informed consent before entering the study.

Participants—Male and female participants of any race aged 12 to 35 years with severe facial acne vulgaris (IGA score of 4) were enrolled in the study. Eligible participants were required to have a minimum of 20 inflammatory lesions, 30 to 120 noninflammatory lesions, and no more than 3 nodulocystic lesions. Specified washout periods were required for participants using topical and oral acne treatments. Exclusion criteria prohibited enrollment of participants with acne conglobata, acne fulminans (secondary acne), or other dermatologic conditions that interfere with treatment or evaluation. Women were excluded if they were pregnant, breastfeeding, or planning a pregnancy during the study.

Efficacy and Safety Assessments—The primary efficacy variable was the percentage change from baseline in total lesion counts (sum of inflammatory and noninflammatory lesions). Secondary efficacy assessments included percentage change from baseline in inflammatory and noninflammatory lesion counts and IGA score (evaluated using a scale of 0 [clear, meaning residual hyperpigmentation and erythema may be present] to 5 [very severe, or highly inflammatory acne covering the face, with nodules and cysts present]).

Digital UV fluorescence photography provided an additional evaluation, as the presence of *P acnes* has been shown to correlate with the intensity of orange-red fluorescence from its metabolites (coproporphyrin III).[14] Few centers were equipped with this system; therefore, the test was performed on only a subset of participants. This reliable, quick, and practical method measures the total spot area, or number

of pixels, associated with UV fluorescent spots that, when reduced, has been found to correlate well with decreased *P acnes* presence in scrub cultures.[15] Although it is not sensitive enough to detect slight changes in *P acnes*, it is highly reliable when large variations occur, indicating clinical relevance.

Safety and tolerability were assessed at each visit through evaluations of local tolerability and the incidence of adverse events (AEs). Erythema, scaling, dryness, and stinging/burning were rated on a scale of 0 (none) to 3 (severe). In addition, a survey of participant satisfaction was completed at the last visit.

Statistical Analyses—All data analyses were carried out according to a pre-established analysis plan. Using results of a prior study,[13] a sample size of 179 participants per group was required to detect a statistically significant difference in the percentage change from baseline in total lesion counts between treatment groups at week 12. This evaluation was based on a 2-tailed test at $\alpha=.05$ and 90% power, an assumption of a median 12% difference with a standard deviation of 35% change from baseline in total lesions, and a dropout rate of 15%.

Three study populations were analyzed: the safety (all randomized participants treated at least once), intention-to-treat (ITT)(all randomized participants dispensed study medication), and per-protocol (all randomized participants without any major protocol deviations) populations. Efficacy analyses and questionnaires were analyzed on the ITT (last observation carried forward) population using the Cochran-Mantel-Haenszel test, and all tests were 2-tailed at $\alpha=.05$. Adverse events and local tolerability were descriptively summarized.

Results

Participant Disposition and Baseline Characteristics—A total of 459 participants were randomized and included in the ITT population: 232 received A/BPO with doxycycline, and 227 received vehicle with doxycycline (Figure 1). Overall, 89.8% of participants completed the study and participant disposition was similar between the 2 groups. Most participants who discontinued did so at their own request (3.0% and 3.1%, respectively) or were lost to follow-up (4.3% and 4.4%, respectively), and very few participants discontinued due to AEs (0.9% and 1.8%, respectively) or lack of efficacy (0% and 0.4%, respectively).

The baseline characteristics of the ITT population are summarized in Table 1. They were similar

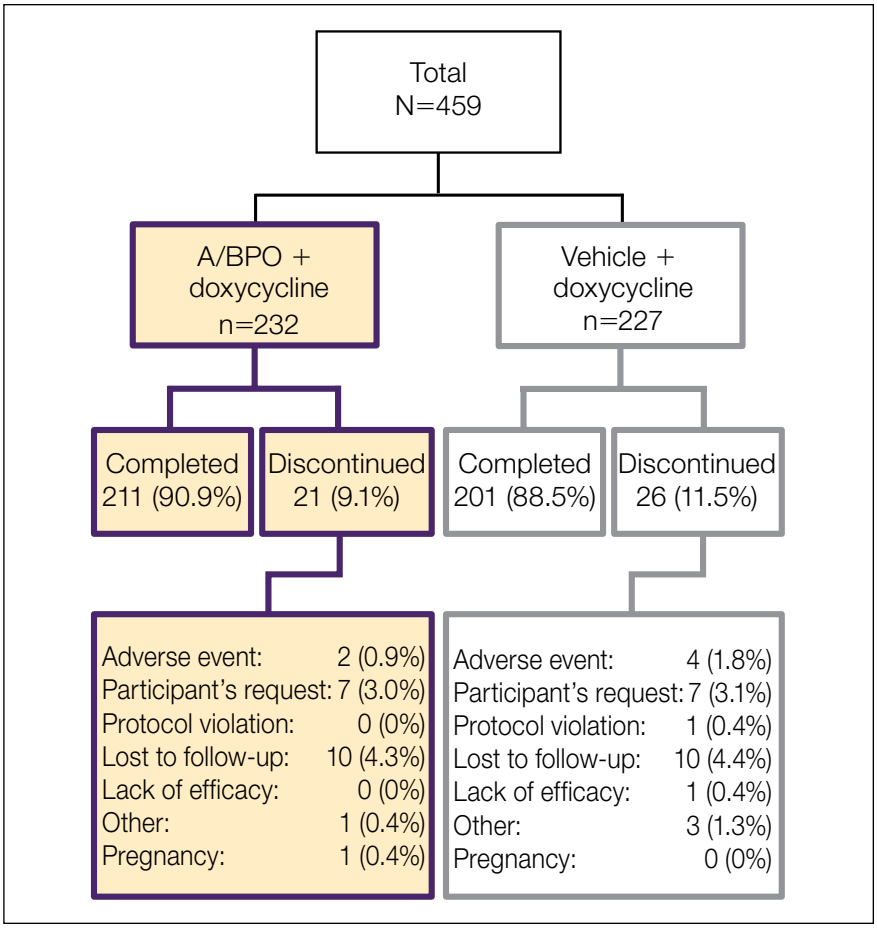

Figure 1. Participant disposition. A/BPO indicates adapalene 0.1%–benzoyl peroxide 2.5%.

Table 1.

Baseline Characteristics (ITT Population)

Demographic/ Clinical Parameter	A/BPO + Doxycycline (n=232)	Vehicle + Doxycycline (n=227)	Total (N=459)
Gender, n (%)			
Male	124 (53.4)	130 (57.3)	254 (55.3)
Female	108 (46.6)	97 (42.7)	205 (44.7)
Age, y			
Mean (SD)	18.6 (5.84)	18.1 (4.92)	18.4 (5.41)
Min, Max	12, 39	12, 38	12, 39
Fitzpatrick skin type, n (%)[a]			
I	8 (3.4)	11 (4.9)	19 (4.1)
II	66 (28.4)	61 (27.0)	127 (27.7)
III	94 (40.6)	87 (38.5)	181 (39.6)
IV	42 (18.1)	45 (19.9)	87 (19.0)
V	12 (5.2)	12 (5.3)	24 (5.2)
VI	10 (4.3)	10 (4.4)	20 (4.4)
Race, n (%)			
White	158 (68.1)	148 (65.2)	306 (66.6)
Black	15 (6.5)	17 (7.5)	32 (7.0)
Asian	1 (0.4)	5 (2.2)	6 (1.3)
Hispanic	55 (23.7)	51 (22.5)	106 (23.1)
Other	3 (1.3)	6 (2.6)	9 (2.0)
Global severity grade (IGA), n (%)			
Severe	232 (100)	227 (100)	459 (100)
Inflammatory lesion count			
Mean (SD)	37.4 (16.3)	37.5 (14.8)	37.4 (15.6)
Min, Max	20, 97	21, 99	20, 99
Noninflammatory lesion count			
Mean (SD)	63.3 (26.6)	62.0 (24.9)	62.7 (25.8)
Min, Max	23, 120	30, 122	23, 122
Total lesion count			
Mean (SD)	101.0 (35.4)	99.5 (32.2)	100.0 (33.8)
Min, Max	49, 201	53, 213	49, 213

Abbreviations: ITT, intention to treat; A/BPO, adapalene 0.1%–benzoyl peroxide 2.5%; SD, standard deviation; IGA, investigator's global assessment.

[a]One participant in the vehicle with doxycycline group was not assessed.

in the 2 groups, with a mean age of 18 years for the overall population, 55.3% male, 66.6% white, and 23.1% Hispanic. Both groups had a similarly high number of inflammatory, noninflammatory, and total lesion counts (mean of 37.4, 62.7, and 100 for the total population, respectively).

Efficacy Evaluation—Percentage change in lesion counts (total, inflammatory, and noninflammatory) from baseline at weeks 2, 4, 8, and 12 are depicted in Figure 2. All counts consistently yielded statistically superior results in favor of A/BPO with doxycycline relative to vehicle with doxycycline.

Percentage reduction in total lesion counts clearly demonstrated that A/BPO with doxycycline was significantly superior to vehicle with doxycycline at all study visits and as early as week 2 at which time one-third of the final effect was already obtained (−21% vs −13%; $P<.001$). At week 12, a benefit of 23% was observed compared with the antibiotic alone (−64% for A/BPO with doxycycline vs −41% for vehicle with doxycycline; $P<.001$). Similarly, A/BPO with doxycycline produced significantly greater reductions in inflammatory lesion counts compared with vehicle with doxycycline, with a rapid onset of action from week 2 (−27% vs −22%; $P=.004$) to week 12 (−72% vs −48%; $P<.001$). Noninflammatory lesion counts also showed a significantly rapid onset of action in percentage reduction from week 2 (−17% vs −10%; $P<.001$) to week 12 (−61% vs −40%; $P<.001$) in favor of A/BPO with doxycycline.

Likewise, for the success rate (defined as the percentage of participants with clear or almost clear ratings on IGA), A/BPO with doxycycline was significantly superior to vehicle with doxycycline from week 8 (9.9% vs 2.6%; $P=.001$) to week 12 (31.5% vs 8.4%; $P<.001$)(Figure 3). Figure 4 depicts the results achieved in a participant with severe acne treated with A/BPO with doxycycline.

Digital UV Fluorescence Photography: Reduction of P acnes—Digital UV fluorescence photographs (Figure 5) were analyzed for 38 participants: 18 in the A/BPO with doxycycline group, and 20 in the vehicle with doxycycline group. The results demonstrated a decrease in total spot area at week 4, with a mean percentage reduction of −60.3% of *P acnes* in the A/BPO with doxycycline group (Figure 6). This reduction continued through week 12 (−73.6%) in the A/BPO with doxycycline group. In contrast, the vehicle with doxycycline group manifested a much smaller decrease (−22% at week 4) that subsequently regressed (−14% at week 12).

Safety Evaluation—Overall the safety and tolerability evaluation of A/BPO with doxycycline was similar to vehicle with doxycycline. Mean tolerability scores for both groups at each visit were all less than 1 (mild)(Figure 7). Except for stinging/burning, tolerability over time was comparable between A/BPO with doxycycline and vehicle with doxycycline, and most participants did not worsen after baseline. For stinging/burning, an expected peak was observed in the A/BPO with doxycycline group during the first 2 weeks of treatment; however, the score diminished through weeks 4 to 12 to a level near baseline.

The incidence of related AEs was low (11.8% in the total population), primarily due to doxycycline intake (9.6% of total participants with gastrointestinal disorders), which was similar between groups, with or without the presence of A/BPO (11.2% vs 12.3% for A/BPO with doxycycline and vehicle with doxycycline, respectively). Few related dermatologic AEs were reported in the A/BPO with doxycycline group—1.7% of participants reported dryness, irritation, and eyelid irritation—as well as the vehicle with doxycycline group—0.4% of participants reported urticaria.

There were no severe AEs during the study. Most AEs were mild or moderate in severity and few of them led to study discontinuation. Three participants discontinued because of gastrointestinal disorders (all in the vehicle with doxycycline group) and 3 discontinued because of dermatologic events (2 in the A/BPO with doxycycline group and 1 in the vehicle with doxycycline group).

Participant Satisfaction—The results of the participant survey were consistent with the investigators' assessments of efficacy and tolerability (Table 2). Most participants were not bothered at all by the treatment side effects and significantly more participants in the A/BPO with doxycycline group compared with the vehicle with doxycycline group expressed overall satisfaction with their combination treatment regimen (76.3% vs 50.3%, respectively; $P<.001$).

Comment

Although combination therapy with a topical retinoid, BPO, and an oral antibiotic is recommended as first-line treatment of all but the most severe recalcitrant acne vulgaris,[2,4] no controlled trials had evaluated this treatment regimen. In our study, the addition of A/BPO to doxycycline hyclate 100 mg provided a faster onset of action and was statistically significantly more efficacious than antibiotic alone ($P<.001$). The combination's superiority was consistently shown by percentage reduction in lesion counts, success rate (IGA), and patient satisfaction. It also was safe and well-tolerated.

The role of *P acnes* in acne inflammation is not completely understood.[4] While our method did

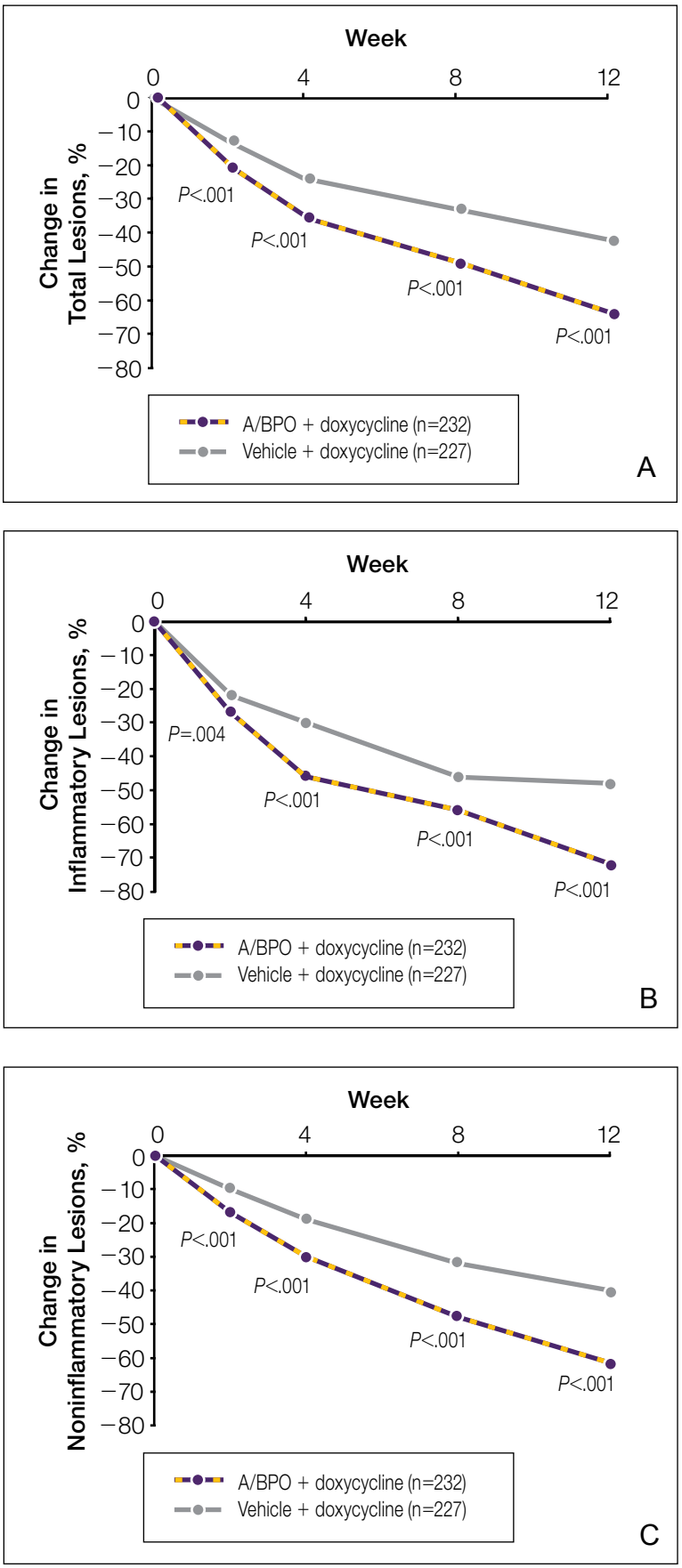

Figure 2. Median percentage reduction in total (A), inflammatory (B), and noninflammatory lesion (C) counts from baseline to week 12 in the intention-to-treat (last observation carried forward) population (N=459). A/BPO indicates adapalene 0.1%–benzoyl peroxide 2.5%.

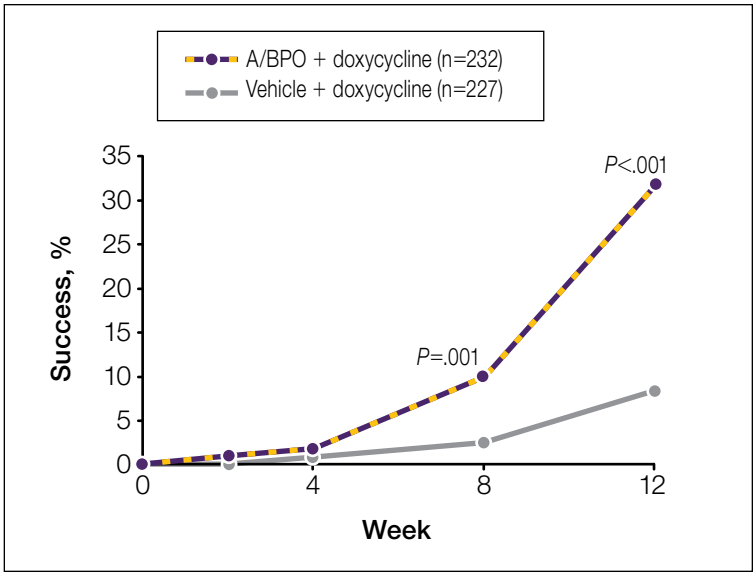

Figure 3. Success rates over 12 weeks (percentage of participants with clear or almost clear ratings on investigator's global assessment) in the intention-to-treat (last observation carried forward) population (N=459). A/BPO indicates adapalene 0.1%–benzoyl peroxide 2.5%.

not include bacterial cultures, our results using the validated digital UV fluorescence photography method[15] indicated a marked sustained suppression of *P acnes* in the A/BPO with doxycycline group, unlike the vehicle with doxycycline group with increases from weeks 4 to 12. Because this method is only sensitive to large reductions in *P acnes*, this finding corroborates the clinical improvement achieved with combination therapy.

Although emergence of *P acnes* antibiotic resistance appears to be a global dilemma, its clinical significance has not yet been clearly identified.[16] In our study, the level of *P acnes* reduction was not directly correlated with the extent of lesion count reduction (approximately a 50% vs 20% difference between groups, respectively). Instead, we hypothesize that antibiotic resistance and the recolonization of *P acnes* observed in the vehicle with

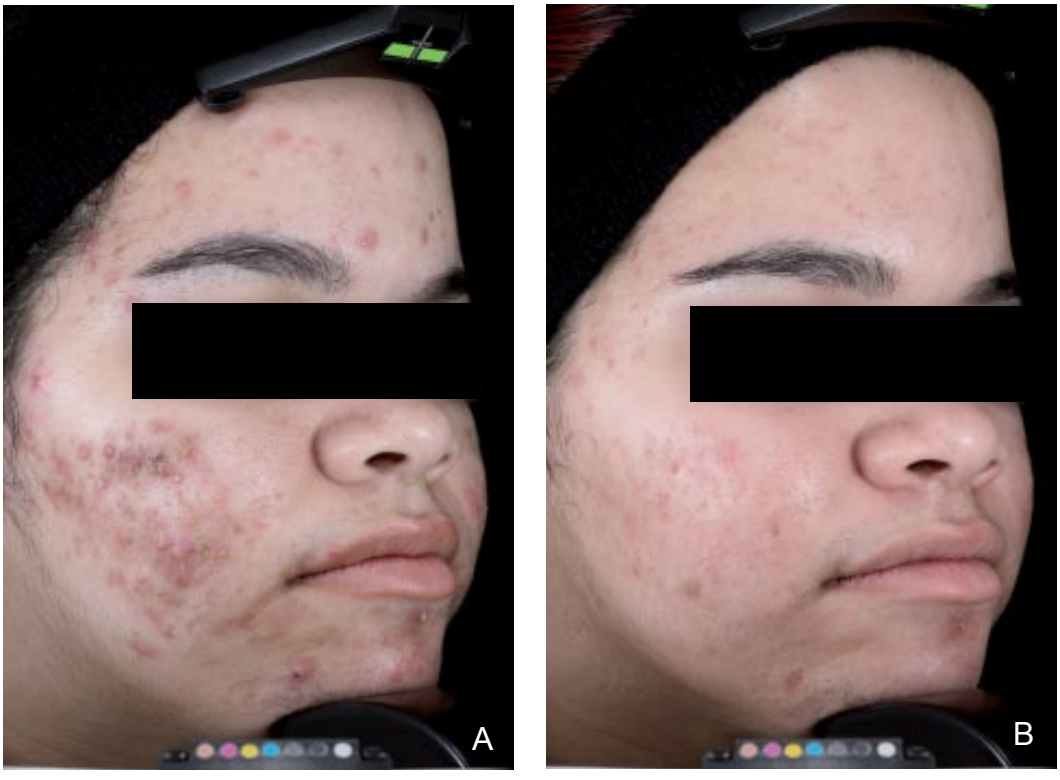

Figure 4. A participant with severe acne vulgaris at baseline (A) and after 12 weeks (B) of adapalene 0.1%–benzoyl peroxide 2.5% gel with doxycycline therapy.

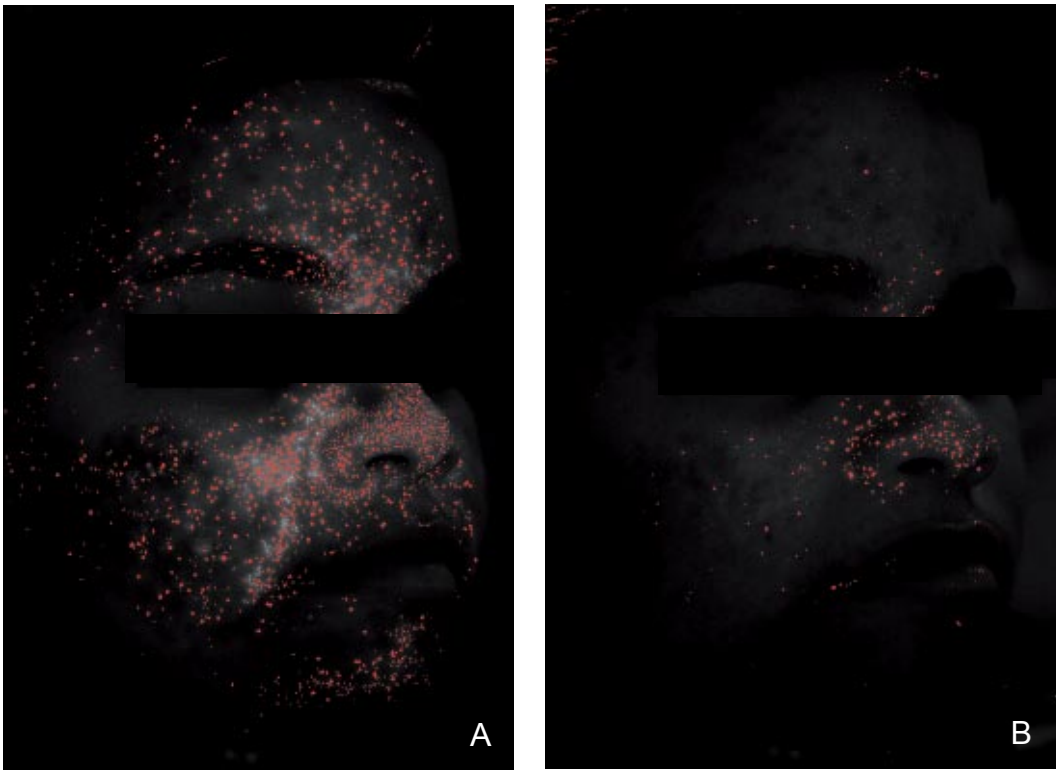

Figure 5. Digital UV fluorescence photographs measuring presence of *Propionibacterium acnes* in a participant with severe acne vulgaris at baseline (A) and after 12 weeks (B) of adapalene 0.1%–benzoyl peroxide 2.5% gel with doxycycline therapy.

doxycycline group could explain this phenomenon, emphasizing the need for combination therapy in the treatment of severe acne vulgaris. Furthermore, we hypothesize that the addition of BPO is essential in reducing the quantity of *P acnes* bacteria.

Prior studies support the use of A/BPO in the treatment of moderate acne.[8,10,12] The anti-inflammatory effect of adapalene used in a regimen with an oral antibiotic also has been shown to reduce inflammatory lesions in moderate to severe acne.[13,17] In this study, only participants with severe acne were included, thus participants had a higher number of lesions at baseline compared to prior A/BPO studies.[8,10,12] Adapalene and

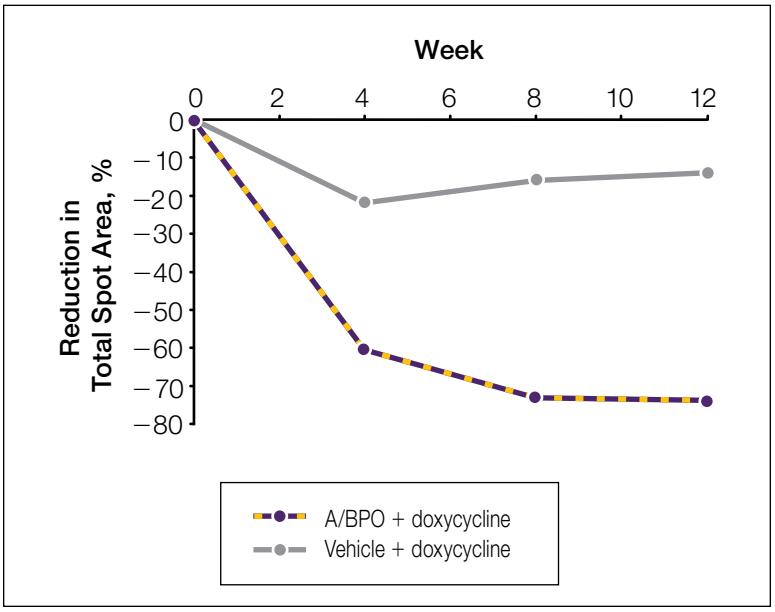

Figure 6. Total spot area of *Propionibacterium acnes* measured by digital UV fluorescence photography. A/BPO indicates adapalene 0.1%–benzoyl peroxide 2.5% (n=38).

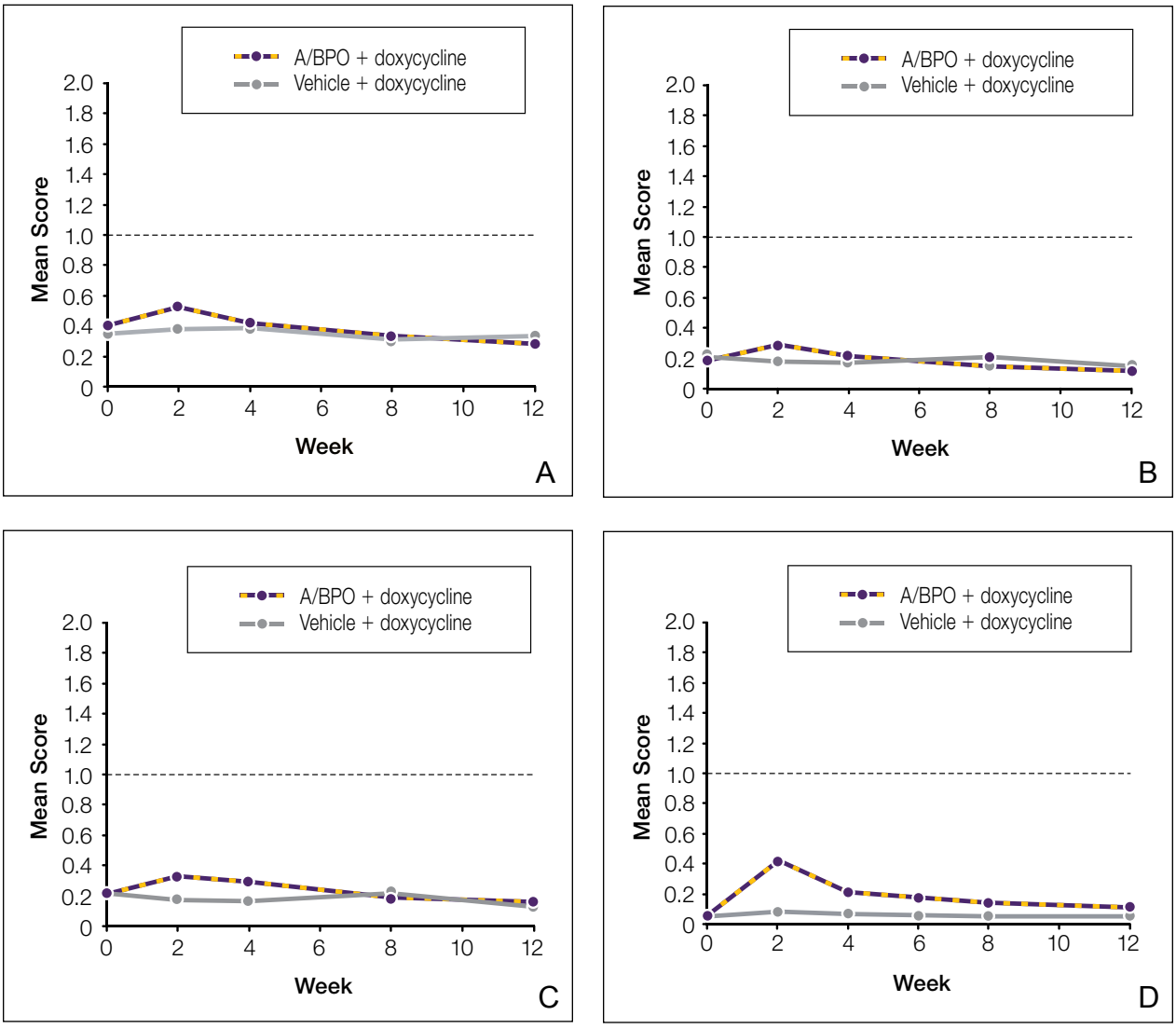

Figure 7. Mean tolerability scores for erythema (A), scaling (B), dryness (C), and stinging/burning (D), measured on a scale of 0 (none) to 3 (severe). A/BPO indicates adapalene 0.1%–benzoyl peroxide 2.5%.

BPO have been shown to act synergistically in the fixed-dose combination[8] and would presumably be superior when combined with doxycycline compared with adapalene alone with doxycycline. An added benefit of more than 10% in lesion count reduction was observed with the A/BPO combination, despite the severity of acne in this population, and an additional 14% of patients were evaluated to be clear or almost clear compared to a prior study.[13] Moreover, A/BPO appears to be more effective as the number of lesions at baseline increases, suggesting that it does not lose efficacy even in severe acne (Tan JK, Gollnick HP, Loesche C, et al; unpublished data; 2009).

Although isotretinoin remains an effective oral therapy for severe recalcitrant nodular acne, its problematic side-effect profile can persist throughout and beyond the course of treatment.[18] In this study, the combined use of A/BPO with an oral antibiotic was safe and relatively well-tolerated. The safety profile of the combination, among other reasons, makes it a compelling and appropriate choice for all but the most severe recalcitrant forms of acne, and generally is supported by guidelines. The European Expert Group on Oral Antibiotics in Acne advocates use of combination therapy preferentially for 3 months or more until clinical improvement,[19] while Thielitz and Gollnick[20] recommend isotretinoin use after 3 months of inadequate response to combination treatment with an oral antibiotic. The conservative duration of this study of doxycycline therapy for 3 months coupled with the addition of topical BPO can avoid the potential for microbial resistance associated with longer term antibiotic therapy.

Table 2.

Participant Satisfaction Questionnaire at Last Visit (ITT Population; N=459)

Survey Question	Response	A/BPO + Doxycycline Group, %	Vehicle + Doxycycline Group, %	*P* Value[a]
How satisfied were you with the time it took for treatment to work?	Satisfied/ very satisfied	70.1	49.5	<.001
How satisfied were you with the effectiveness of the treatment?	Satisfied/ very satisfied	72.3	48.8	<.001
How do you feel about yourself since starting your treatment?	A lot better/ much better	67.0	47.7	<.001
How bothered were you by the treatment side effects?	Not bothered at all	61.4	70.8	NS
Overall, are you satisfied with the treatment?	Satisfied/ very satisfied	76.3	50.3	<.001
Would you consider using this treatment again?	Yes	86.8	71.8	<.001

Abbreviations: ITT, intention to treat; A/BPO, adapalene 0.1%–benzoyl peroxide 2.5%; NS, not significant.
[a]*P* value for between-treatment difference, evaluated by Cochran-Mantel-Haenszel test based on ridit scores stratified by pseudocenter.

Conclusion

The results of this study provide evidence regarding the efficacy and safety of combining A/BPO with doxycycline in the first-line treatment of severe acne vulgaris. Clinical benefit was observed by week 2, and the combination treatment was safe, well-tolerated, and yielded high participant satisfaction.

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